Clinical Policy Title:	penicillamine
Policy Number:	RxA.082
Drug(s) Applied:	Cuprimine®
Original Policy Date:	02/07/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

Penicillamine is a chelating agent indicated for the treatment of:

- Wilson's disease;
- Cystinuria as add on therapy; and
- Severe, active rheumatoid arthritis (RA) in patients who have failed to respond to an adequate trial of conventional therapy.

Limitation(s) of use: Available evidence suggests that penicillamine is not of value in ankylosing spondylitis.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
penicillamine (Cuprimine®)	Cystinuria	1-4 gm/day PO in 4 divided doses	4 gm/day
	Wilson's disease	750-1,500 mg/day PO in divided doses	2 gm/day
	RA	125-250 mg PO once daily	1.5 gm/day

Dosage Forms

- Cuprimine®: capsule, 250 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. Wilson's Disease (must meet all)**:**

1. Member has a diagnosis of Wilson's disease confirmed by one of the following:
   a. Presence of Kayser-Fleischer rings and low serum ceruloplasmin (CPN) levels and elevated 24-hour urinary copper levels;
   b. Molecular genetic confirmation; or
   c. Liver biopsy confirmation;
2. Medical justification supports inability to use generic penicillamine tablets (e.g., contraindication to excipients);

3. Dose does not exceed 2 gm (8 capsules) per day.

Approval duration
Commercial: 12 months
Medicaid: 12 months

B. Cystinuria (must meet all)**:**

1. Member has a diagnosis of cystinuria;
2. Member has tried and failed a urinary alkalinizing agent (e.g., potassium citrate) at maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
3. Medical justification supports inability to use generic penicillamine tablets (e.g., contraindication to excipients);
4. Dose does not exceed 4 gm (16 capsules) per day.

Approval duration
Commercial: 12 months
Medicaid: 12 months

C. Rheumatoid Arthritis (must meet all)**:**

1. Member has a diagnosis of RA;
2. Member meets one of the following (a or b):
   a. Failure of three (3) or more consecutive months of methotrexate;
   b. If intolerance or contraindication to methotrexate, failure of three (3) or more consecutive months of sulfasalazine, leflunomide, or hydroxychloroquine unless contraindicated or clinically significant adverse effects are experienced;
3. Medical justification supports inability to use generic penicillamine tablets (e.g., contraindication to excipients);
4. Dose does not exceed:
   a. Initial therapy: 250 mg (1 capsule) per day for at least the first month;
   b. Maintenance therapy: 1.5 gm (6 capsules) per day.

Approval duration
Commercial: 12 months
Medicaid: 12 months

II. Continued Therapy Approval

A. All Indications in Section 1 (must meet all)**:**

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy (*see Appendix D*);
3. If request is for a dose increase, new dose does not exceed (a, b, or c):
   a. Wilson's disease: 2 gm (8 capsules per day) per day;
   b. RA: 1.5 gm per day (6 capsules per day);
   c. Cystinuria: 4 gm (16 capsules) per day.

Approval duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key

CPN: Ceruloplasmin
FDA: Food and Drug Administration
PO: By Mouth
RA: Rheumatoid Arthritis

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
penicillamine (Depen® Titratabs)	Wilson's disease: 250 mg PO four times daily; adjust to achieve urinary copper excretion 0.5-1 mg/day Cystinuria: 250 mg PO once daily; increase gradually to 1-2 gm/day in 4 divided doses and adjust to achieve target urinary cysteine excretion RA: 125-250 mg PO once daily; increase at 1-3 month intervals by 125-250 mg/day according to response and tolerance (typical maintenance range: 500-750 mg/day) – if no improvement at 1-1.5 gm/day after 3-4 months, therapy should be discontinued as a response is unlikely to occur.	Wilson's disease: 2 gm/day (750 mg/day if pregnant) Cystinuria: 5 gm/day RA: 1.5 gm/day
potassium citrate	Cystinuria*: 60-80 mEq/day divided into 3-4 doses (15–20 mL/day); titrate to achieve a urine pH within target range 7-7.5	See regimen
methotrexate (Rheumatrex®)	RA: 7.5 mg/week PO, SC, or IM or 2.5 mg PO Q12 hr for 3 doses/week	30 mg/week
sulfasalazine (Azulfidine®)	RA: 2 gm/day PO in divided doses	3 gm/day
leflunomide (Arava®)	RA: 100 mg PO once daily for 3 days, then 20 mg PO once daily	20 mg/day
hydroxychloroquine (Plaquenil®)	RA* <u>Initial dose:</u> 400 – 600 mg/day PO once daily <u>Maintenance dose:</u> 200 – 400 mg/day PO once daily	600 mg/day

Therapeutic alternatives are listed as Brand name®(generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - History of penicillamine-related aplastic anaemia or agranulocytosis, nursing, patients with RA and cystinuria who are pregnant (exceptions can be made for certain patients with cystinuria), patients with RA and history or other evidence of renal insufficiency.

- Boxed Warning(s):
  - None

APPENDIX D: General Information

- Although the prescribing information for penicillamine does not include an absolute maximum dose for Wilson's disease, it notes it is seldom necessary to exceed a dose of 2 gm/day. In addition, both the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver do not recommend doses higher than 1.5 gm/day due to potential for rapid and often irreversible neurological deterioration.
- In cystinuria, initial therapy includes high fluid intake, sodium and protein restriction, and urinary alkalinization. The preferred agent for urinary alkalinization is potassium citrate. Other agents that can be used include potassium bicarbonate, acetazolamide, and sodium bicarbonate or citrate.
- In RA, failure of methotrexate or disease-modifying antirheumatic drugs is defined as less than a 50% decrease in swollen joint count, less than a 50% decrease in tender joint count, and less than a 50% decrease in erythrocyte sedimentation rate (ESR), or less than a 50% decrease in C-reactive protein (CRP).
- Examples of positive response include:
  - Wilson's disease: reduction in 24-hour urinary copper excretion;
  - Cystinuria: reduction in urinary cysteine level; and
  - RA: improvement in symptoms.
- For female patients who are actively attempting to conceive:
  - MTX is a pregnancy category X and is absolutely contraindicated in pregnancy and is not recommended for female patients attempting to conceive.
  - Acitretin should not be used in females attempting to conceive because the drug is esterified in fat remaining in the system for up to three (3) years and has the potential to cause birth defects.
  - Cyclosporine is associated with low birth weights; thus, cyclosporine is not appropriate for female patients attempting to conceive.

References

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4. Pearle MS, Goldfarb DS, Assimos DG, et al. Medical management of kidney stones: AUA guideline. Published 2014. Available at: http://www.auanet.org/guidelines/medical- management-of-kidney-stones-(2014). Accessed February 1, 2021.
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7. Roberts E., Schilsky M. AASLD Practice Guidelines: Diagnosis and Treatment of Wilson Disease: An Update. Hepatology, June 2008; 47: 2089-2111.
8. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2021. Available at: http://www.clinicalpharmacology-ip.com/. Accessed February 1, 2021.
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Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Updated line of business	04/2020	05/2020
Policy reviewed and updated. 1. Clinical policy title and lines of business updated. 2. Criteria for initial approval and duration of approval updated. 3. Continued therapy criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance…". 4. Appendix D updated. 5. References updated.	02/01/2021	03/09/2021